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Third Preliminary Amendment

Applicant(s): Guo et al.

Serial No. 10/539,241

Filed: 16 June 2005 (Parent: 16 December 2003)

For: pRNA CHIMERA

Amendments to the Claims

This listing of claims replaces all prior versions, and listings, of claims in the above-identified application:

1. (Currently Amended) A polyvalent multimeric complex comprising a plurality of chimeric pRNA chimeras, ~~at least one pRNA chimera comprising (a) a pRNA region and (b) a spacer region comprising a biologically active RNA, the spacer region covalently linked at its 5' and 3' ends to the pRNA region monomers, each said chimeric pRNA monomer independently comprising a heterologous component.~~
2. (Currently Amended) The polyvalent multimeric complex of claim 1 wherein the heterologous component of at least one chimeric pRNA monomer comprises a biologically active RNA [is] selected from the group consisting of a ribozyme, a siRNA, an RNA aptamer, an antisense RNA and a peptide nucleic acid (PNA).
3. (Currently Amended) The polyvalent multimeric complex of claim 1 wherein the heterologous component of at least one chimeric pRNA monomer comprises an end-labeling agent, the RNA aptamer binds a cell surface receptor.
4. (Currently Amended) The polyvalent multimeric complex of claim ~~[[1]]~~ 3 wherein the end-labeling agent is selected from the group consisting of biotin, pCp, DIG, SH group and phosphate RNA aptamer binds an endosomal disruption agent.
5. (Currently Amended) The polyvalent multimeric complex of claim 1 wherein at least one of the chimeric pRNA monomers is a circularly permuted pRNA the RNA aptamer binds to a virus.
6. (Currently Amended) The polyvalent multimeric complex of claim ~~[[5]]~~ 1 wherein at least one of the chimeric pRNA monomers is a non-circularly permuted pRNA the virus is an adenovirus.

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7. (Currently Amended) The polyvalent multimeric complex of claim [[5]] 1 wherein at least one of the chimeric pRNA monomers incorporates at least one nucleotide analog or modified nucleotide ~~the virus comprises a polynucleotide that operably encodes a therapeutic agent.~~

8. (Currently Amended) The polyvalent multimeric complex of claim 7, wherein the nucleotide analog or modified nucleotide is selected from the group consisting of a 2'-F-2' deoxy nucleotide derivative, a phosphorothioate, a 2'-O-methyl ribonucleotide, a peptide nucleic acid (PNA) ~~claim 1, comprising a pRNA chimera comprising an RNA aptamer that binds a cell surface receptor; a pRNA chimera comprising an RNA aptamer that binds an endosomal disruption agent; and a pRNA chimera comprising a therapeutic RNA.~~

9-16. (Cancelled)

17. (Currently Amended) A method for delivering a therapeutic agent to a cell comprising:
contacting the cell with the polyvalent multimeric complex of claim 1, wherein the heterologous component of a first chimeric pRNA monomer chimera of the polyvalent multimeric complex comprises a therapeutic agent and the heterologous component of a second chimeric pRNA monomer chimera of the polyvalent multimeric complex comprises a biologically active moiety that specifically binds a component of the cell membrane, such that the polyvalent multimeric complex is taken up by the host cell.

18. (Previously Amended) The method of claim 17 wherein the component of the cell membrane to which the polyvalent multimeric complex binds is a receptor, and wherein the polyvalent multimeric complex is taken up by the cell via receptor-mediated endocytosis.

19-27. (Cancelled)

28. (New) A non-circularly permuted chimeric pRNA monomer comprising 5' and 3' ends, wherein at least one of said 5' and 3' ends comprises a heterologous component.

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29. (New) The pRNA monomer of claim 28 wherein the heterologous component comprises antisense RNA.

30. (New) The pRNA monomer of claim 28 wherein the heterologous component comprises an aptamer.

31. (New) The pRNA monomer of claim 28 wherein the heterologous component comprises a labeling agent.

32. (New) The pRNA monomer of claim 31 wherein the labeling agent is selected from the group consisting of biotin, pCp, DIG, SH group and phosphate.

33. (New) The pRNA monomer of claim 32 comprising at least one nucleotide analog or modified nucleotide.

34. (New) The pRNA monomer of claim 33, wherein the nucleotide analog or modified nucleotide is selected from the group consisting of a 2'-F-2' deoxy nucleotide derivative, a phosphorothioate, a 2'-O-methyl ribonucleotide, a peptide nucleic acid (PNA).

35. (New) A chimeric pRNA monomer comprising at least one nucleotide analog or modified nucleotide.

36. (New) The chimeric pRNA monomer of claim 35 which is a circularly permuted pRNA.

37. (New) The chimeric pRNA monomer of claim 35 wherein the nucleotide analog or modified nucleotide is selected from the group consisting of a 2'-F-2' deoxy nucleotide derivative, a phosphorothioate, a 2'-O-methyl ribonucleotide, a peptide nucleic acid (PNA).

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38. (New) A method for making a polyvalent multimeric complex comprising:

providing a first RNA monomer comprising a first biologically active component, said first RNA monomer further comprising nucleotide sequence A and nucleotide sequence b';

providing a second RNA monomer comprising a second biologically active component, said second RNA monomer further comprising nucleotide sequence B and nucleotide sequence a', wherein said first and second RNA monomers are transcomplementary RNAs in that nucleotide sequences A and a' are complementary, and nucleotide sequences B and b' are complementary; and

combining said first and second RNA monomers to permit intermolecular interaction to yield the polyvalent multimeric complex.

39. (New) The method of claim 38 wherein the first RNA monomer comprises a chimeric pRNA monomer comprising right loop A and left loop b', and wherein the second RNA monomer comprises a chimeric pRNA monomer comprising a right loop B and a left loop a'.

40. (New) A method for making a polyvalent multimeric complex comprising:

providing a first RNA monomer comprising a first biologically active component, said first RNA monomer further comprising nucleotide sequence A and nucleotide sequence b';

providing a second RNA monomer comprising a second biologically active component, said second RNA monomer further comprising nucleotide sequence B and nucleotide sequence c'; and

providing a third RNA monomer comprising a third biologically active component, said third RNA monomer further comprising nucleotide sequences C and nucleotide sequence a'; wherein said first, second and third RNA monomers are transcomplementary RNAs in that nucleotide sequences A and a' are complementary, nucleotide sequences B and b' are complementary, and nucleotide sequences C and c' are complementary; and

combining said first, second and third RNA monomers to permit intermolecular interaction to yield the polyvalent multimeric complex.

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41. (New) The method of claim 40 wherein the first RNA monomer comprises a chimeric pRNA monomer comprising right loop A and left loop b'; the second RNA monomer comprises a chimeric pRNA monomer comprising a right loop B and a left loop c'; and the third RNA monomer comprises a chimeric pRNA monomer comprising right loop C and left loop a'.
42. (New) The method of claim 38 or 40 wherein at least one of the biologically active components comprises a targeting agent.
43. (New) The method of claim 38 or 40 wherein at least one of the biologically active components comprises a therapeutic agent.
44. (New) The method of claim 38 or 40 wherein at least one of the biologically active components comprises a labeling agent.
45. (New) The method of claim 38 or 40 wherein at least one RNA monomer comprises at least one nucleotide analog or modified nucleotide.
46. (New) The method of claim 45 wherein the nucleotide analog or modified nucleotide is selected from the group consisting of a 2'-F-2' deoxy nucleotide derivative, a phosphorothioate, a 2'-O-methyl ribonucleotide, a peptide nucleic acid (PNA).
47. (New) The method of claim 38 or 40 wherein at least one of the chimeric pRNA monomers is a non-circularly permuted pRNA.
48. (New) The method of claim 38 or 40 wherein at least one of the chimeric pRNA monomers is a circularly permuted pRNA.